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10/722,176	11/24/2003	Tariq M. Rana	20336-00016	3047

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EXAMINER	
CHONG, KIMBERLY	
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1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,19-28,30 and 33-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,19-28,30 and 33-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/13/2009 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 02/13/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/15/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/15/2008, claims 14, 19-28, 30 and 33-44 are pending and currently under examination in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "…a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "…disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

Claim 14 is drawn to a delivery mixture comprising a delivery agent consisting of a dendrimer mixed with a nucleic acid effective to mediate RNAi. The instant claim and specification fail to provide adequate written description of the broad genus of nucleic

acid molecules that is commensurate in scope with the breadth of the instant invention: a nucleic acid effective to mediate RNAi.

The specification as filed discloses in Example 2 a siRNA molecule mixed with a dendrimer that was able to silence CDK9 expression in HeLa cells. The specification does not adequately describe a representative number of species in the broad genus of nucleic acids that are commensurate in scope to what is claimed. The instantly claimed genus is large, encompassing microRNA, short hairpin RNA and DNA:RNA hybrid molecules all of varying lengths and chemical compositions that when mixed with a delivery agent effectively mediates RNAi. A review of the specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention. The specification does not describe any structural features that would be common to members of nucleic acids that are capable of the claimed function and further the specification fails to describe a representative number of species within the genus of nucleic acids to constitute a description of the entire genus claimed.

MPEP §2163 states, in part "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process." Moreover, MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when …

the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of nucleic acid molecules effective in an amount to mediate RNAi.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker,* 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 19-28, 30 and 33-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szoka et al. (US Patent No. 5,661,025 of record cited on PTO Form 892 filed 02/26/2008), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) Olejnik et al. (cited on PTO Form 892 filed 08/23/05) and Grigoriev et al. (cited on PTO Form 892 filed 08/23/05).

The instant claims are drawn to a delivery mixture comprising a 2 to 5 generation dendrimer mixed with an amount of a nucleic acid effective to mediate RNAi, wherein the nucleic acid is an RNA molecule, wherein the RNA is a miRNA, a shRNA or a siRNA, wherein the siRNA comprises a sense and antisense strand complementary to a target mRNA sequence, wherein the sense and antisense strands are crosslinked, wherein the crosslink is psoralen, wherein the siRNA comprises a modification at the 3'OH terminus, wherein the modification is a photocleavable biotin, wherein the dendrimer is PAMAM, wherein the dendrimer is a generation 4 dendrimer, wherein the dendrimer to nucleic acid ration is as recited in claims 40-42 and wherein the siRNA is from 16-30, 23-32 or 21 nucleotides in length.

Szoka et al. teach DNA, RNA and RNA:DNA hybrid oligonucleotide molecules wherein the molecules are mixed with PAMAM dendrimers having generations 2 to 5 (see columns 9 and 10 and see Table 2). Szoka et al. teach the delivery mixture comprising a dendrimer and oligonucleotide is capable of delivering the oligonucleotide molecule to subcellular component of a cell (see column 5). Szoka et al. do not teach mixing an amount of nucleic acid effective to mediate RNAi with a dendrimer, do not specifically teach the siRNA to dendrimer concentration at a ratio of between about 10 ug to 1 mg or 20 ug to 40 ug or about 40 ug and do not teach incorporation of a photocleavable biotin or psoralen crosslinks.

Tuschl et al. teach siRNA molecules, 19-23 nucleotides in length comprising 3' 2 nucleotide overhangs that are effective at mediating RNAi wherein the nucleotides of the sense strand and antisense strand are complementary to the target gene (see page

6, lines 8-15 and Figure 14). Likewise, McManus et al. teach shRNA and microRNA which are effective at mediating RNAi (see page 740).

Olejnik et al. teach oligonucleotides comprising photocleavable biotin (see page 362).

Grigoriev et al. teach incorporation of psoralens into oligonucleotide for formation of psoralen crosslinks (see Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the delivery mixture comprising a dendrimer as taught by Szoka et al. for delivering a siRNA, microRNA or shRNA as taught by Tuschl et al. and McManus et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modifications such as photocleavable biotin and crosslinks using psoralens, into the siRNA.

One would have been motivated to make a delivery mixture comprising a dendrimer and a siRNA or a microRNA or shRNA because Tuschl et al. and McManus et al. both teach such nucleic acid compounds are more efficient at silencing gene expression and are very useful for determining the function of a gene. In probing gene function and inhibition of gene expression, one of skill in the art would be motivated to use the most efficient methodology for mediating RNAi efficiently in cells, thereby allowing elucidation of gene function. Because siRNA is an inhibitory nucleic acid molecule, one would expect to encounter similar issues in delivery to cells as with the previously known oligonucleotides and therefore one would be motivated to use a

delivery mixture comprising a dendrimer because the goal for RNAi is optimal delivery of the siRNA and enhanced cellular uptake by the cells.

Szoka et al. teach testing various dendrimer to oligonucleotide ratios to determine the optimal amount to use for efficient delivery to cellular compartments (see Table 4). Szoka et al. do specifically teach an oligonucleotide to dendrimer concentration at a ratio of between about 10 ug to 1 mg or 20 ug to 40 ug or about 40 ug, but do teach various ratios of oligonucleotide to dendrimer ratio therefore demonstrating the routine nature of testing various ratios for optimization of the most efficient ratio for delivery and gene inhibition. Therefore because the use of dendrimers in a delivery mixture, as claimed by the instant invention, were known to add benefits to delivery of oligonucleotides molecules to cells, one would have been motivated to make a delivery mixture comprising siRNA and test various ranges for the optimal concentration.

One would have been further motivated to incorporate a photocleavable biotin modification at the end of the siRNA contained in the delivery mixture comprising a dendrimer because Olejnik et al. teach incorporation of a photocleavable biotin into a oligonucleotide provides a simple method for purification of oligonucleotides (see abstract). Additionally, Olejnik et al. teach incorporation of a photocleavable biotin allows isolation of nucleic acids after synthesis and after cleavage of the biotin moiety, the functional nucleic acids can be used in further methods (see page 361). Further, one would have been motivated to incorporate psoralens, as taught by Grigoriev et al., into the siRNA contained in the delivery mixture to increase the target specificity of the

siRNA to the target gene once the siRNA is delivered to cells. Grigoriev et al. teach addition of psoralen derivatives to oligonucleotides increase the antisense target affinity and half-life by crosslinking the antisense oligonucleotide to the target (see page 3501).

Finally, one would have a reasonable expectation of success at making a delivery mixture comprising a dendrimer and a siRNA given Szoka et al. teach efficient delivery of nucleic acids into cellular compartments using dendrimer and given one would expect the siRNA nucleic acid molecule to be delivered similarly. Additionally, it is a matter of routine skill in the art to use the dendrimer and siRNA of Tuschl et al. at different concentrations to determine the effective ratio of dendrimer to oligonucleotide for efficient delivery into cells. Further, one would have had a reasonable expectation of success at incorporating a photocleavable biotin and psoralen crosslinks into the siRNA contained in the delivery mixture because Olejnik et al. teach synthesis of an oligonucleotide comprising a photocleavable biotin and teach efficient purification of the oligonucleotide and photocleavable of the biotin moiety and further Grigoriev et al. teach efficient inhibition of gene expression using cross linked nucleic acids.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 102 - withdrawn

The rejection of claims 14, 19, 38, 39 and 43 under 35 U.S.C. 102(b) as being anticipated by Szoka et al. (US Patent No. 5,661,025) is withdrawn.

Re: Claim Rejections - 35 USC § 103 - maintained

The rejection of claims 14, 19-28, 30 and 33-44 under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (Clinical Cancer Research 2001 of record cited on PTO Form 892 filed 02/26/2008), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) Olejnik et al. (cited on PTO Form 892 filed 08/23/05) and Grigoriev et al. (cited on PTO Form 892 filed 08/23/05) and evidenced by Milhem et al. (International Journal of Pharmaceutics 2000, Vol. 197: 239-241 of record cited on PTO Form 892 filed 02/26/2008) is maintained for the reasons of record.

The claims have been amended to recite the dendrimer is mixed with “an amount of a nucleic acid effective to mediate RNA interference (RNAi)". This new limitation would have been rejected in the previous action as Tuschl et al. teach using siRNA at effective amounts that mediate RNAi.

Applicant’s arguments in the response filed 02/13/2009 are acknowledged but not found persuasive. Applicant argues that Sato et al. do not disclose evidence of effective RNA interference or delivery of siRNA and Milhem et al. do not disclose or suggest the use of G4 PAMAM dendrimers wit an amount of nucleic acid effective to mediate RNAi and therefore the combinations of the references neither teaches nor makes obvious the presently claimed invention.

Applicant's arguments are not convincing because the combination of the cited references as a whole do in fact make the claimed invention obvious to one of ordinary skill in the art. Applicant is correct in that Sato et al. do not teach effective RNAi or delivery of RNAi, however Sato et al. teach a generation 4 dendrimer, that when mixed with an antisense oligonucleotide, can efficiently deliver said oligonucleotide to cells in vitro and in vivo. There is nothing in the Sato et al. reference that would discourage one of skill in the art away from the use of a generation 4 dendrimer to deliver nucleic acids. Sato et al. teach dendrimers form very stable complexes with negatively charged nucleic acids, are less cytotoxic and are efficient at delivering nucleic acids even in the presence of serum proteins in cells by protecting the nucleic acid from degradation by exonucleases. Given that Sato et al. teach efficient delivery of nucleic acids that were mixed with a generation 4 dendrimer, one of skill in the art would want to use such an efficient delivery mixture for delivery of siRNA that is shown by Tuschl et al. are effective at mediating RNAi, particularly given it was well known at the time of filing that RNAi was shown to be more efficient at silencing gene expression.

Moreover, it was well known at the time of filing of the instant invention and the field of therapeutic applications using nucleic acids was replete with references discussing the difficulties of delivering nucleic acids to cells which ranged from the toxicity of viral delivery systems, inefficient delivery of nucleic acids to cells and tissues and degradation of nucleic acids by serum proteins found in the cell. Sato et al. has shown very specifically that a generation 4 dendrimer can help to overcome some of the disadvantages of delivering nucleic acids to cells, therefore a person of ordinary skill in

the art would have good reason to use such a delivery agent to deliver nucleic acid, such as siRNA, effective to mediate RNAi and would have expected to be able to deliver the nucleic acids to cells and tissues.

The examiners reliance on Milhem et al. was only evidentiary for the use of G4 PAMAM dendrimers as efficient drug delivery vehicles and Milhem et al. was not used to teach any of the claimed limitations, such as delivery of a nucleic acid effective to mediate RNAi.

Thus, the rejection of record is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service

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